In re Application of: Gila MAOR
Serial No.: 10/627,739
Filed: July 28, 2003
Office Action Mailing Date: June 15, 2007

Examiner: Barnhart, Lora Elizabeth
Group Art Unit: 1651
Attorney Docket: 26243

## REMARKS

Reconsideration of the above-identified application in view of the amendments above and the remarks following is respectfully requested.

Claims 1-9 and 11-107 are in this Application. Claims 12, 13, 15, 16 and 24-103 were withdrawn from consideration. Claims 6 and 8 have been rejected under 35 U.S.C. § 112 first paragraph. Claims 1-5, 7-9, 11, 14, 17-21, 23, 104-107 have been rejected under 35 U.S.C. § 102(b). Claims 1-5, 7-9, 11, 14, 17-23 and 104-107 have been rejected under 35 U.S.C. § 103(a). Claim 107 has now been canceled. Claims 1, 2, 6, 21, 22, 23 and 104 have been amended herewith. New claim 108 has been added herewith.

### *Drawings*

Replacement figures in compliance with 37 CFR 1.121(d) are attached herewith to overcome the objection of the Examiner.

A Petition for Color Drawings, three sets of color drawings and the appropriate fee is also attached herewith.

### *35 U.S.C. § 112, First Paragraph, Rejections*

The Examiner has rejected claims 6 and 8 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The Examiner states that the claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the claimed invention.

Specifically, the Examiner states that claim 6 is drawn to a method of making cultured chondrocytes comprising culturing chondrocytes isolated from mandibular condyle "using culturing conditions devoid of a three dimensional support". However, the Examiner states, the chondrocytes are plated in "35 mm six-well culture dishes"

which are considered to be three-dimensional support and the chondrocytes cannot grow without some solid support. The Examiner's rejection is respectfully traversed.

However, **claim language must be analyzed, not in a vacuum, but in light of:**

(A) The content of the particular application disclosure;

(B) The teachings of the prior art; and

**(C) The claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made.**

It is well established in the relevant art (i.e., in the art of cell/tissue culturing) that three dimensional support/scaffold or matrix relates to a three dimensional matrix composed of any material and/or shape that (a) allows cells to attach to it (or can be modified to allow cells to attach to it); and (b) allows cells to grow in more than one layer (see e.g., U.S. Pat. No. 4,963,489 column 3 lines 53-58); Lu L. Zhu X. Valenzuela RG. Currier BL. Yaszemski MJ. Biodegradable polymer scaffolds for cartilage tissue engineering. *Clinical Orthopaedics & Related Research. (391 Suppl):S251-70, 2001 Oct;* attached). Thus, it is clear that 35 mm plates, though being three dimensional objects, cannot be construed as three dimensional supports for culturing.

Not withstanding the above and in order to render explicit what was already implicit, Applicants have elected to add a functional language to claim 6 for clearly stating that the claimed absence of three dimensional support is for establishing a monolayered culture. Support for this can be found on page 44 lines 19-20 of the instant specification.

In view of the above arguments and claim amendment, Applicants respectfully request withdrawal of the rejection in this case.

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***35 U.S.C. § 102 Rejections***

***Bhalerao et al.***

The Examiner has rejected claims 1-5, 7-9, 11, 14, 17-21, 23 and 104-107 under 35 U.S.C. 102(b) as being anticipated by Bhalerao et al. [Bhalerao et al., Tissue and Cell (1995) 27:369-382].

Specifically, the Examiner states that Bhalerao et al. teaches incubating mouse mandibular condyles in DMEM/F-12 containing 0.1 % collagenase, a protease, and agitating the tissue to liberate cells into the medium. Bhalerao et al. teaches pooling all liberated cells, pelleting them, and culturing them in fresh medium for 3 passages over 9 days. The Examiner further states that the culture conditions taught by Bhalerao et al. utilize culture flasks which are not coated with any biomolecules.

The Examiner's rejection is respectfully traversed. Claim 1 has now been amended.

The cells described in the art of Bhalerao et al. are not chondrocytes. As stated in the Abstract and shown on page 375 beginning on line 3 and figure 7 of Bhalerao et al., cells described therein are genetically transformed for immortalization and express collagen types I, II, and III but not aggrecan and link protein, and as such cannot be considered genuine chondrocytes which can be used to produce hyaline cartilage. Bhalerao et al. admit that the cells generated according to their teachings are not differentiated chondrocytes (see lines 15 and 17 of the abstract, respectively) *"...they do not resemble dedifferentiated chondrocytes"*) and *"...represent transitional differentiation stages of the progenitor cells of the mandibular condyle"*. They even explicitly associate this lack of differentiation to chondrocytes by the genetic immortalization. See page 380, right column, third paragraph *"The reason why the SM cells do not differentiate further is not clear. Whether certain factors are lacking in our experimental set up or whether the SV40 large T protein is preventing further differentiation is not known. Large T antigen has been shown to block cellular differentiation"*. The authors then elaborate on the possible mechanism of blockade of differentiation, thereby explicitly teaching away from the claimed cultured

chondrocytes which express Type II collagen but not Type I collagen (see page 48 lines 18-21 and Figures 3E-G of the instant application). As described in the instant specification page 51 lines 1-6 and in the attached papers by Castagnola et al. [Castagnola et al., J of Cell Biology (1988) 106: 461-467] and McDougall et al. [McDougall et al., J Bone Miner Res. (1996) 11(8): 1130-8], published well before filing of the instant application, chondrocytes which are suitable for generating hyaline cartilage are only those which do not express collagen type I. Therefore, the teachings of Bhalerao et al. teach away from- and are in sharp contrast with the claimed methodology which teaches generation of chondrocytes (primary) which express collagen type II and not collagen type I. Clearly, by expressing collagen types I the cells of Bhalerao et al. cannot be considered cultured chondrocytes as claimed and as such cannot be used to anticipate the claimed invention.

In order to expedite prosecution and to render explicit what was already implicit, claim 1 has been amended to clarify that the chondrocytes express collagen type II and not collagen type I, which as previously described are markers of differentiated chondrocytes (support can be found in see page 48 lines 18-21 and Figures 3E-G of the instant application).

In addition, new claim 108 reciting primary cells has been added. Support for this claim language can be found in page 47 line 18 and in page 50 lines 22-23 of the instant specification.

Claim 23 has been amended to recite neonatal mammal. Support for the added limitation can be found in Page 32 line 29 of the instant specification.

As to the claimed method of isolating chondrocytes (subject of claim 104 and dependent therefrom; as well as claim 2 and dependents therefrom), this is profoundly different than the teachings of Bhalerao et al. Briefly, Bhalerao et al. teach enzymatic treatment of condyle cells from a mouse mandibular tissue and pooling of all the cells, such that the resultant population comprises both chondrocytic as well as non-chondrocytic cells (i.e., myocytes and fibroblasts) which make up the condyle. This is

in sharp contrast to the claimed invention where the mandibular condyle tissue is first treated to deplete all non-chondrocytic cells (i.e., fibroblasts and/or myocytes); and then the treated (i.e., modified) tissue is enzymatically treated to recover i.e., isolate the chondrocytes.

This is further in sharp contrast to Examiner's assertion as if the pending claims do not recite chondrocyte purification. It is the collection/isolation of chondrocytes from the condyle modified tissue, which allows the collection of homogeneous chondrocytes free of fibroblasts and/or myocytes.

Not withstanding the above and in order to expedite prosecution, Claims 2 and 104 have now been amended so as to render explicit what was already implicit that the chondrocytes are isolated from the modified tissue which does not comprise fibroblasts and myocytes (corresponding to now canceled claim107).

In view of the above claim amendments, arguments and remarks Applicants believe to have overcome the 35 U.S.C. § 102(b) rejections.

### *35 U.S.C. § 102 Rejections*

### *Landesberg et al.*

The Examiner has rejected claims 1-5, 7-9, 14, 17-19, 23 and 104-107 under 35 U.S.C. 102(b) as being anticipated by Landesberg et al. [Landesberg et al., Calcified Tissue International (1995) 56:71-77].

Specifically, the Examiner states that Landesberg et al. teaches incubating calf mandibular condyles in F-12 medium containing 0.1 % trypsin and then in F-12 medium containing 0.2 % collagenase, agitating the tissue to liberate cell into the medium, filtering and collecting the cells by centrifugation before culturing them. Landesberg et al. teaches that the MCCs isolated by their procedure comprise hypertrophic chondrocytes. The Examiner further states that the culture conditions taught by Landesberg et al. utilize culture flasks which are not coated with any biomolecules.

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The Examiner's rejection is respectfully traversed. Claim 1 has now been amended.

The cells described in the art of Landesberg et al. are not chondrocytes. As described on page 73 beginning on line 18 and Figure 1 of Landesberg et al., cells described therein are calf mandibular condyle cells separated into 5 cellular fractions (sorted by their cell size). According to the teachings of Landesberg et al., all cell fractions showed type I collagen (see page 75, left column, lines 1-10) while only minute amounts of type II collagen indicating that the culture cannot be considered genuine chondrocytic culture which can be used to produce hyaline cartilage. As described in the instant specification on page 51 lines 1-6 and in the attached papers by Castagnola et al. [Castagnola et al., J of Cell Biology (1988) 106: 461-467] and McDougall et al. [McDougall et al., J Bone Miner Res. (1996) 11(8): 1130-8], published well before filing of the instant application, chondrocytes which are suitable for generating hyaline cartilage are only those which do not express collagen type I. Therefore, the teachings of Landesberg et al. are in sharp contrast to the claimed methodology which teaches generation of chondrocytes (primary) which spontaneously differentiate to express collagen type II and not collagen type I. Clearly, by expressing collagen type I the cells of Landesberg et al. cannot be considered cultured hyaline chondrocytes as claimed and as such cannot be used to anticipate the claimed invention.

In order to expedite prosecution and to render explicit what was already implicit, claim 1 has been amended to clarify that the chondrocytes express collagen type II and not collagen type I, which as previously described are markers of hyaline cartilage forming chondrocytes.

As to the method of isolating chondrocytes (subject of claim 104 and dependents therefrom; as well as claim 2 and dependents therefrom), this is profoundly different than the teachings of Landesberg et al. Briefly, Landesberg et al. teach harsh enzymatic treatment condyle tissue from a calf mandibular tissue and pooling of the

cells, such that the resultant population comprises both chondrocytic as well as non-chondroytic cells (i.e., myocytes and fibroblasts) which make up the condyle. See for instance, page 71 right column *"Isolation of Mandibular Condylar Cells"* explicitly stating *"All of the cells liberated by the enzymatic digestions were then filtered through 40 μM mesh filter and then collected by centrifugation..."* This is in sharp contrast to the claimed invention where the mandibular condyle tissue is first treated to deplete all non chondrocytic cells (i.e., fibroblasts and/or myocytes); and then the treated (i.e., modified) tissue is enzymatically treated to recover the chondrocytes. This is further in sharp contrast to Examiner's assertion as if the pending claims do not recite chondrocyte purification. It is the isolation of chondrocytes from the condyle modified tissue, which allows the collection of homogeneous chondrocytes free of fibroblasts and/or myocytes.

Not withstanding the above and in order to expedite prosecution, Claims 2 and 104 has now been amended so as to render explicit what was already implicit that the chondrocytes are isolated from the modified tissue which does not comprise fibroblasts and myocytes (support is recited above).

In view of the above claim amendments, arguments and remarks Applicants believe to have overcome the 35 U.S.C. § 102(b) rejections.

### *35 U.S.C. § 103 Rejections*

The Examiner has rejected claims 1-5, 7-9, 11, 14, 17-23 and 104-107 under 35 U.S.C. 103(a) as being unpatentable over Bhalerao et al. [Bhalerao et al., Tissue and Cell (1995) 27:369-382] taken in view of Palmer et al. [Palmer et al., Arthritis Research (2002) 4: 226-231].

Specifically, the Examiner states that Bhalerao et al. teaches incubating mouse mandibular condyles in DMEM/F-12 containing 0.1 % collagenase, a protease, and agitating the tissue to liberate cells into the medium. Bhalerao et al. teaches pooling the liberated cells, pelleting them, and culturing them in fresh medium for 3 passages

over 9 days. The Examiner further states that the culture conditions taught by Bhalerao et al. utilize culture flasks which are not coated with any biomolecules. The Examiner has conceded that Bhalerao et al. do not teach passaging their cells 4 times.

The Examiner further states that Palmer et al. teach that chondrocytes may be subcultured several times and that chondrocytes at passage 3 are equivalent in experiments to those at passage 5.

Furthermore, the Examiner states that a person of ordinary skill in the art would have had a reasonable expectation of success in passaging the cells of Bhalerao et al. 4 times because Palmer et al. teaches that chondrocytes may be passaged at least 5 times.

The Examiner's rejection is respectfully traversed. Claims 21 and 22 have now been amended.

As stated hereinabove (see Applicants arguments the 35 USC § 102 anticipation by Bhalerao et al.), Bhalerao fails to teach the method of isolating chondrocytes from a mandibular tissue (subject of claims 104 and dependents therefrom; as well as claim 2 and dependents therefrom), by teaching cell pooling rather than chondrocyte isolation from the chondyle population. In addition, Bhalerao et al. do not teach culturing the isolated chondrocytes so as to obtain cultured chondrocytes which express collagen type II but not collagen type I.

Therefore, it is Applicants strong position that the teachings of Bhalerao et al. cannot be used alone or in combination with the mere passaging described by Palmer et al. to arrive at the claimed invention.

In view of the above claim amendments, arguments and remarks Applicants believe to have overcome the 35 U.S.C. § 103(a) rejections.

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In view of the above amendments and remarks it is respectfully submitted that claims 1-5, 7-9, 11, 14, 17-23 and 104-6 and 108 are now in condition for allowance. A prompt notice of allowance is respectfully and earnestly solicited.

Respectfully submitted,

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Date: October 18, 2007

***Enclosures:***

- Two-Month Extension Fee;
- Formal Drawing Transmittal Sheet;
- Replacement Drawings Sheets;
- Additional Claims Transmittal Sheet;
- Petition for Color Drawings and Three Sets of Color Drawings;
- Lu et al reference